Surgery Today (2018) 48:502–509
https://doi.org/10.1007/s00595-017-1616-5

ORIGINAL ARTICLE

A new postoperative pain management (intravenous acetaminophen: Acelio®) leads to enhanced recovery after esophagectomy: a propensity score-matched analysis

Yu Ohkura[1,2] · Junichi Shindoh[1,2] · Masaki Ueno[1,2] · Toshiro Iizuka[2,3] · Shusuke Haruta[1] · Harushi Udagawa[1,2]

Received: 9 August 2017 / Accepted: 27 November 2017 / Published online: 12 December 2017

Abstract

Purposes To investigate the efficacy of postoperative scheduled intravenous acetaminophen to reduce the opioid use and enhance the recovery after esophagectomy.

Methods A propensity score-matched population was created using the 93 and 69 consecutive patients who underwent esophagectomy for esophageal cancer before and after the introduction of postoperative scheduled intravenous acetaminophen, and the short-term clinical outcomes were compared.

Results Significant defervescence was demonstrated in the Acetaminophen group (A-group) compared with control group (C-group) during the perioperative period ($p < 0.05$), whereas no significant differences were observed in the postoperative inflammatory parameters. The incidence of postoperative complications was similar between the groups. The number of PCA pushes and the frequency of using other non-opioid analgesics were significantly smaller in the A-group than in the C-group ($p < 0.05$). Both daily and cumulative opioid uses were significantly smaller in the A-group than in the C-group ($p < 0.05$). The time to first flatus was significantly shorter in the A-group than in the C-group ($p < 0.001$). The day of first walking after surgery was significantly earlier in the A-group than in the C-group (1.0 versus 2.0 days, $p = 0.003$). The ICU stay (2.86 versus 3.61 days, $p < 0.001$) and the hospital stay (21.5 versus 26.0 days, $p = 0.061$) tended to be shorter in the A-group than in the C-group.

Conclusions Postoperative scheduled intravenous acetaminophen decreased the rate of opioid use without increasing the intensity of postoperative pain and may be a feasible new pain management option in the enhanced recovery after surgery protocol following esophagectomy.

Keywords Esophageal cancer · Acetaminophen · Pain management · Propensity score matching · ERAS

Introduction

Growing attention is being paid to perioperative management using the enhanced recovery after surgery (ERAS) protocol, which aims to reduce surgical invasiveness and postoperative complications and shorten the hospital stay. As a postoperative pain management strategy for the ERAS protocol, patient-controlled analgesia (PCA) using epidural anesthesia has recently been recommended [1–3]. The combined use of low-dose opioid with local anesthetics has been demonstrated to be very effective for postoperative pain control. Meanwhile, the use of opioids has been associated with the risk of suppressing gastrointestinal (GI) motility and postoperative nausea and vomiting (PONV). We have reported that postoperative scheduled intravenous (IV) acetaminophen after gastrectomy may reduce the use of opioids and might be associated with enhanced GI motility and a decreased incidence of postoperative nausea and vomiting after gastrectomy [4]. However, the efficacy of scheduled IV acetaminophen after esophageal surgery remains to be established.

✉ Yu Ohkura
yu.ohkura107@gmail.com

1 Department of Gastroenterological Surgery, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan

2 Okinaka Memorial Institute for Medical Research, Tokyo, Japan

3 Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan

Therefore, we examined the efficacy of scheduled IV acetaminophen in combination with epidural anesthesia for achieving an early recovery after esophagectomy with the aim of reducing the postoperative use of opioids.

Materials and methods

This single-center intervention study was conducted to evaluate the efficacy of scheduled acetaminophen IV infusion for postoperative pain control and the subsequent ability to reduce opioid use after esophagectomy for esophageal cancer, as well as the usefulness of acetaminophen for the facilitation of ERAS. We introduced a scheduled postoperative IV acetaminophen regimen in January 2016. A total of 174 consecutive patients with esophageal cancer were identified from the prospectively constructed database at the Department of Gastroenterological Surgery, Toranomon Hospital, between October 2014 and December 2016. Of the 103 patients treated before the introduction of the acetaminophen regimen, 93 patients, after excluding 6 who did not receive epidural anesthesia and also excluding 4 who had already used IV acetaminophen, were allocated to the control (C-) group, while 69 of the 71 patients treated after the introduction of the regimen were allocated to the acetaminophen (A-) group, after excluding 1 patient not receiving epidural anesthesia and another who did not use IV acetaminophen.

The patients in both groups were matched for demographic variables using propensity scores, and the following variables in the matched groups consisting of 69 patients each (Fig. 1) were compared: (1) postoperative course (fever pattern and inflammatory responses); (2) postoperative complications; (3) postoperative pain assessment; (4) clinical efficacy (improvement in GI motility and incidence of PONV); and (5) ERAS (the day of first walking and the duration of the intensive-care unit [ICU] stay and postoperative hospital stay). Disease was staged according to the UICC TNM grading system, 7th editions [5]. Postoperative complications were graded according to the Clavien–Dindo classification system [6], with grade ≥ 2 events recorded as complications. Postoperative liver dysfunction was graded according to the Common Terminology Criteria for Adverse Events, with grade ≥ 3 events (defined as $\geq 5 \times$ the upper limit of normal) recorded as complications [7]. The pain assessment was based on the number of PCA pushes for epidural anesthesia, postoperative opioid use, and the frequency of using non-opioid analgesics, including NSAIDs and pentazocine hydrochloride. Improvement in the GI motility, was assessed based on the time to the first defecation/flatus after operation. The effects on PONV were assessed based on the number of doses of metoclopramide after the operation and the rate of early withdrawal from epidural anesthesia. The ERAS assessment was based on the day of first walking and the duration of the ICU stay and postoperative hospital stay.

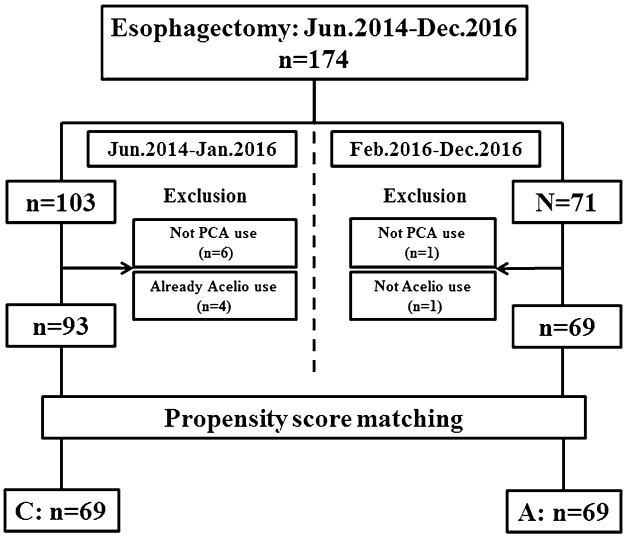

Fig. 1 Patients tree. Patients in both groups were matched for demographic variables using propensity scores, and the following variables in the matched groups consisting of 69 patients each

This study was approved by the Institutional Review Board of Toranomon Hospital, and informed consent was obtained from all of the patients.

Operative procedure

We performed esophagectomy with three- or two-field lymph node dissection depending on the degree of progression and surgical risks. The operative thoracic approach is video-assisted thoracoscopic surgery (VATS) or thoracotomy, and the abdominal approach is hand-assisted laparoscopic surgery (HALS) or open laparotomy. On the thoracoscopic approach, 5- and 12-mm ports were inserted through the second and fourth intercostal spaces on the anterior axillary line (assistant's ports), respectively, and an 11-mm port was inserted through the fifth intercostal space on the middle axillary line (camera port) and the fourth (5 mm) and sixth (11 mm) intercostal spaces on the posterior axillary line (operator's ports). In the HALS procedure, an approximately 8-cm incision was made at the upper abdominal midline. Then, an 11-mm port was inserted in the lower abdomen and a 5-mm port in the left hypochondrium [8–11]. According to the UICC TNM grading system, 7th edition [5], we preserved the thoracic duct in clinical stage (cStage) I cases and resected it in cStage $\geq$ II cases. The reconstruction technique was either gastric tube, ileocolon, or jejunal interposition.

Epidural anesthesia

Epidural anesthesia was administered as a continuous infusion of a 300-ml mixture of ropivacaine (288 ml) and fentanyl (6 ampules, 0.1 mg/2 ml) at a rate of 2–5 ml/h depending on the pain intensity, starting immediately after the operation, with 1–3 ml PCA (i-Fuser; JMS, Tokyo, Japan) as rescue analgesia.

Acetaminophen

An IV infusion of acetaminophen (Acelio Intravenous Injection®; TERUMO Co. Ltd., Tokyo, Japan) was started on the day of the operation at 1000 mg/dose every 6 h for patients weighing ≥ 50 kg or at 500 mg/dose every 6 h for patients weighing < 50 kg at consistent times every day. The infusion continued until hospital day 5, and then, the oral intake and oral medications were started on postoperative day 7.

Statistical analyses

Statistical analyses were performed using the Statistic Package for Social Science (SPSS) software program, version 19.0 J for Windows (SPSS Inc., Chicago, IL, USA). Intergroup comparisons were performed using Pearson's chi-squared test, McNemar's test, Fisher's exact test, or the Mann–Whitney *U* test, as appropriate. In this study, we performed propensity score matching to minimize the selection bias between patients treated before and after the introduction of the acetaminophen regimen. The propensity score matching was calculated from a multivariate logistic regression model, including the age, sex, body mass index (BMI), American Society of Anesthesiologist's (ASA) score, clinical tumor staging, tumor localization, extent of lymphadenectomy, and operative approach. With the propensity score estimated, 69 pairs of patients before and after the introduction of the acetaminophen groups were matched using a 1:1 nearest neighbor matching algorithm. For all analyses, differences were considered statistically significant when $p < 0.05$.

Results

Patient characteristics

Table 1 summarizes the patient characteristics of the two groups. Both groups were similar with respect to the age, sex, BMI, ASA score, clinical stage, tumor localization, extent of lymphadenectomy, operative procedure, operative approach, resection/preservation of thoracic duct and reconstruction technique, as well as the operative outcomes, including the operative duration and blood loss.

Anti-inflammatory effect

Figure 2a shows the postoperative fever patterns in both groups. These statistical analyses compared the value on each day. Although no significant intergroup differences were observed in the fever intensity immediately after operation, the A-group showed faster defervescence and a significantly lower temperature between postoperative day (POD) 1 and POD 3. Figure 2b, c shows the trends in the postoperative inflammatory response [white blood cell (WBC) count and C-reactive protein (CRP) level] in both groups. With regard to the postoperative inflammatory responses, blood testing showed no significant differences in the WBC or CRP values between the groups.

Postoperative complications

Table 2 summarizes the postoperative complications in the two groups. Postoperative complications were observed in 30 of 69 (43.4%) patients in the C-group and 26 of 69 (37.7%) patients in the A-group, with no significant differences between the groups ($p = 0.488$). No significant differences were also found in the incidence of individual complications. Concerning liver dysfunction, a known adverse reaction to acetaminophen, no significant increase was observed in its postoperative incidence, demonstrating the safety of the current regimen. No significant differences were also observed in the incidence of CD grade ≥ 3 complications, which occurred in 20 (29.0%) patients in the C-group and 15 (21.7%) patients in the A-group ($p = 0.328$). No deaths were reported in either group.

Assessment of postoperative analgesia

The trend in the daily number of PCA pushes for postoperative epidural anesthesia up to POD 3 was recorded for pain assessment in Fig. 3a. A significantly smaller frequency of PCA pushes in the A-group was noted each day between the day of operation (POD 0) and POD 2 ($p < 0.05$), indicating a significant reduction in pain. Figure 3b shows the changes in the postoperative opioid use. Each column denotes the daily opioid use, while the polygonal lines denote the cumulative opioid use. The daily opioid use was significantly smaller in the A-group between POD 0 and POD 2 ($p < 0.001$). Consistent with this, a significant reduction of about 32% in the cumulative opioid use was also noted in the A-group ($p < 0.001$). The number of bolus doses of other non-opioid analgesics was recorded for pain assessment (Table 3). The frequency of using non-opioid analgesics outside the postoperative acetaminophen regimen was also significantly smaller in

Table 1 Clinicopathological characteristics of the 138 patients

	C-group ($n=69$)	A-group ($n=69$)	p value
Age (years), median (range)	63.9 (32–81)	62.0 (39–83)	0.242
Sex			0.834
Male	54	55	
Female	15	14	
Body mass index (kg/m^2)	20.8 (13.8–31.0)	20.9 (14.7–27.8)	0.647
ASA-PS			0.312
1	15	14	
2	45	51	
3–	9	4	
cStage (7th)			0.490
I (IA, IB)	26	31	
II (IIA, IIB)	17	12	
III (IIIA, IIIB, IIIC)	23	21	
IVa	3	5	
Tumor Localization			0.375
Ce	1	4	
Ut	9	14	
Mt	31	29	
Lt	17	12	
Ae	1	3	
EGJ	10	7	
Lymphadenectomy			0.166
D0	3	3	
D2	25	15	
D3	41	51	
Operative approach (thoracic)			1.000
Open	10	10	
VATS	59	59	
Operative approach (abdomen)			0.857
Open	23	24	
HALS	46	45	
Thoracic duct			0.721
Preservation	25	23	
Resection	44	46	
Reconstruction organ			0.682
Gastric tube	36	38	
Iliocolon	25	26	
Jejunum	8	5	
Operative duration (min)	578.0 (235–767)	555.0 (303–764)	0.240
Amount of bleeding (ml)	382 (0–1113)	358 (0–1363)	0.195

ASA American Society of Anesthesiologists physical status classification, *VATS* video-assisted thoracic surgery, *HALS* hand-assisted laparoscopic surgery

the A-group (4.57 doses) than in the C-group (8.64 doses; $p<0.001$).

Assessment of GI motility and PONV (Table 3)

With regard to improvement in the postoperative GI motility, the median time to first flatus after the operation was 3.4 days in the C-group versus 2.6 days in the A-group, indicating a significant improvement in the GI motility in the A-group ($p<0.001$). In contrast, the mean time to first defecation after operation in the A-group (4.2 days) was about half a day shorter than in the C-group (4.5 days), a non-significant difference ($p=0.140$).

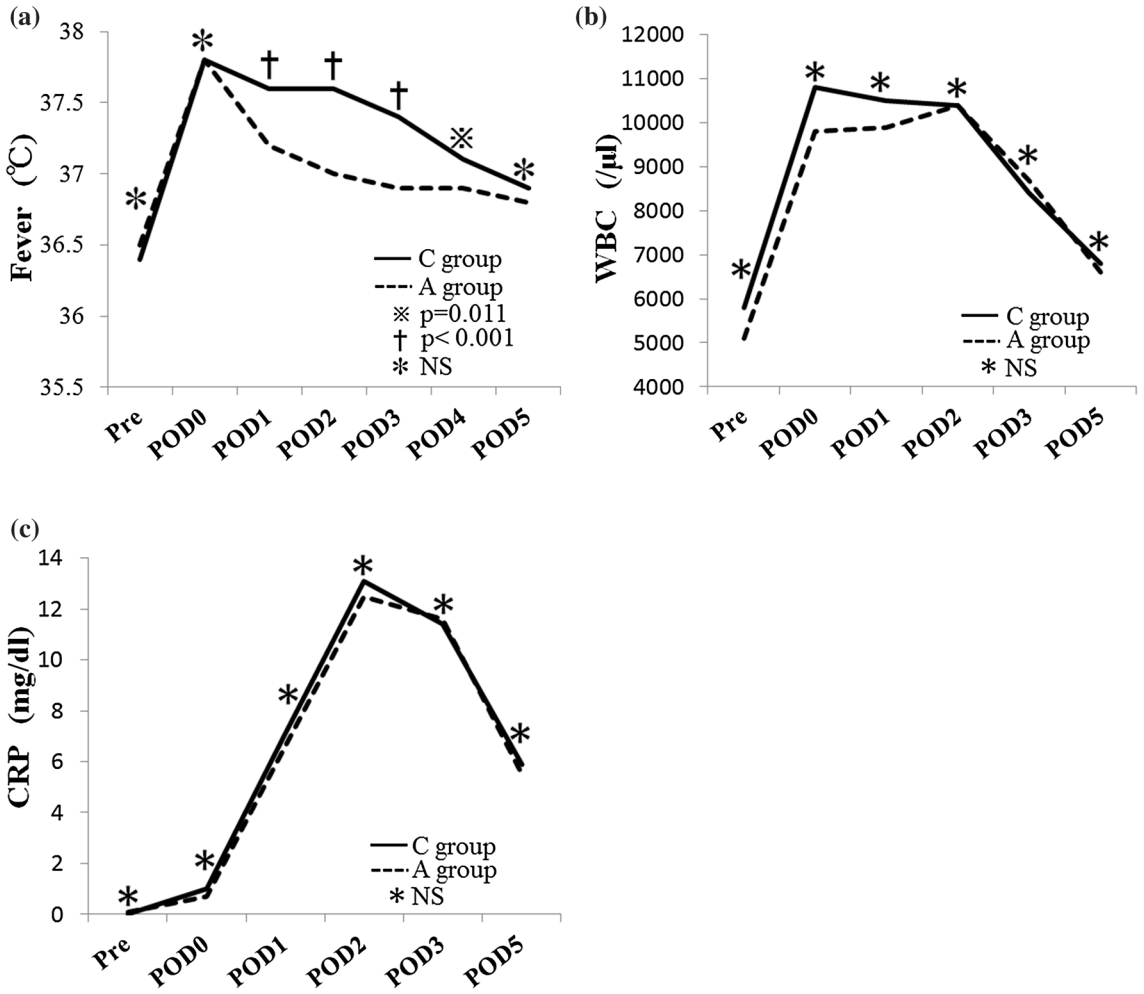

Fig. 2 **a** Postoperative temperature. The postoperative fever patterns in both groups. The A-group showed faster defervescence and significantly greater decreases in fever between POD 1 and POD3. **b** Postoperative inflammatory response of white blood cell counts. The postoperative WBC patterns in both groups. With regard to postoperative inflammatory responses, WBC value showed no significant difference between the groups. **c** Postoperative inflammatory response of C-reactive protein value. The postoperative CRP patterns in both groups. With regard to postoperative inflammatory responses, CRP value showed no significant difference between the groups

Table 2 Postoperative complications

	C-group ($n=69$)	A-group ($n=69$)	p value
Morbidity (CD Grade II or higher)	30 (43.4%)	26 (37.7%)	0.488
Anastomotic leakage	9	7	0.595
Chylothorax	4	6	0.527
Cervical lymphorrhea	5	8	0.382
Bleeding	1	2	0.559
Other	14	7	0.154
Elevated liver enzyme levels (CTCAE Grade 3 or higher)	5	6	0.753
Clavien–Dindo classification (Grade III or higher)	20 (29.0%)	15 (21.7%)	0.328
Mortality	0	0	1.000

CD Clavien–Dindo classification, *CTCAE* common terminology criteria for adverse events

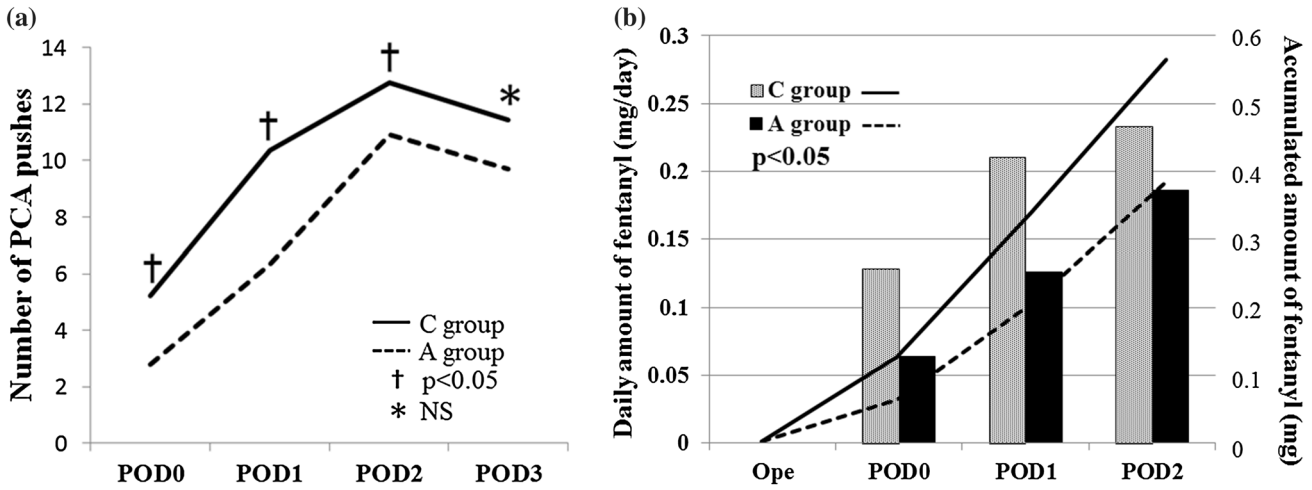

Fig. 3 **a** Number of PCA pushes. The change in the daily number of PCA pushes up to POD3. A significantly reduced frequency of PCA pushes in A-group was noted each day in the period between the day of operation (POD0) and POD3 ($p < 0.05$). **b** Opioid usage in PCA. The daily opioid use while the polygonal lines denote cumulative opioid uses. Daily opioid uses were significantly reduced in A-group each day between POD0 and POD2 ($p < 0.05$). Consistent with this, a significant reduction about 32% in the cumulative opioid use was also noted in A-group ($p < 0.05$)

Table 3 Effect of postoperative intravenous acetaminophen

	C-group ($n=69$)	A-group ($n=69$)	p value
Assessment of postoperative analgesia			
Number of doses of IV analgesic	8.64	4.57	<0.001
GI motility and PONV			
Time to first flatus after operation (days)	3.4	2.6	<0.001
Time to first defecation after operation (days)	4.5	4.2	0.140
The number of doses of IV metoclopramide	8 (11.6%)	4 (5.8%)	0.207
Interruption of PCA	7 (10.1%)	1 (1.4%)	0.030
Early recovery after surgery			
Time to first walking after operation (days)	2.0	1.0	0.003
Postoperative ICU stay (days)	3.61	2.86	<0.001
Postoperative hospital stay (days)	26.0	21.5	0.061

IV intravenous, *GI* gastrointestinal, *PONV* postoperative nausea and vomiting, *PCA* patient-controlled analgesia, *ICU* intensive-care unit

As for the effects on PONV, the number of patients who used at least one dose of metoclopramide for postoperative nausea did not differ significantly between the groups ($p=0.207$). In contrast, the number of patients who had to discontinue epidural anesthesia due to PONV was significantly smaller in the A-group (1.4%) than in the C-group (10.1%) ($p=0.030$). Regarding the GI motility, no significant differences were noted between gastric tube reconstruction and ileocolon reconstruction. Similarly, no significant differences in PONV were noted between the reconstruction organs.

Early recovery after esophagectomy (Table 3)

With regard to improvement with the ERAS, the median time to first walking after the operation was 2.0 days in the C-group versus 1.0 day in the A-group, indicating significant improvement in the A-group ($p=0.003$). When limited to the VATS + HALS procedure, this parameter was 2.0 days in the C-group (40 patients) versus 1.0 day in the A-group (39 patients), indicating significant improvement in the A-group ($p<0.001$). In addition, when limited to gastric tube reconstruction, this parameter was 2.0 days in the C-group (36 patients) versus 1.0 day in the A-group (38

patients), indicating significant improvement in the A-group ($p = 0.006$).

The median length of postoperative intensive-care unit (ICU) stay in the A-group was one-and a half-day, significantly shorter than in the C-group (2.86 versus 3.61 days, $p < 0.001$). The mean length of postoperative hospital stay in the A-group (21.5 days) was about 5 days shorter from in the C-group (26.0 days), but the difference between the two groups was not significant ($p = 0.061$).

Discussion

In this study, we attempted to establish a new postoperative pain management regimen involving the use of scheduled intravenous acetaminophen after esophagectomy. We obtained promising results regarding the ability of this new management approach to reduce the rate of opioid use without increasing the intensity of postoperative pain, and this regimen is feasible with the ERAS protocol after esophagectomy.

We suggested in our previous report that postoperative scheduled IV acetaminophen might reduce the use of opioids and be associated with enhanced GI motility and a decreased incidence of PONV after gastrectomy [4]. However, the efficacy of scheduled IV acetaminophen in the field of esophageal surgery has been unclear. At Toranomon Hospital, we have introduced scheduled postoperative IV infusion of non-opioid analgesic acetaminophen combined with epidural anesthesia with the aim of reducing opioid use without increasing the intensity of postoperative pain to facilitate postoperative recovery. To benefits have been noted when using the scheduled IV acetaminophen regimen after esophagectomy for esophageal cancer. First, the acetaminophen regimen did not increase the frequency or severity of postoperative complications. Second, the acetaminophen regimen can reduce postoperative opioid use without increasing the intensity of postoperative pain, leading to a reduced incidence of PONV, earlier rising from bed and improved GI motility, thereby facilitating an enhanced postoperative recovery after surgery.

Bjorkmann et al. [12] suggested that acetaminophen exerts antipyretic and analgesic effects through its strong action on the central nervous system, but has limited anti-inflammatory actions in peripheral tissues. In own series as well, no hematological evidence of improved inflammatory responses was seen, but we did observe significant defervescence after the operation. Defervescence leads to improvement in fever-related subjective symptoms, but there are concerns about masking postoperative complications. The acetaminophen regimen may make the fever pattern ambiguous, but it does not affect the hematology data, thereby enabling the early diagnosis and treatment of complications through regular blood monitoring. Indeed, given that there were no significant differences in the morbidity rates between the two groups, postoperative scheduled IV acetaminophen may not be related to the increased severity of complications. In addition, the rate of liver dysfunction, a known adverse reaction to acetaminophen, was not significantly increased, just as was observed in the field of gastric surgery [13, 14].

Major factors hampering the ERAS protocol include pain, GI dysfunction, and immobility. Although these three factors interact with each other, it is particularly important to control postoperative pain to improve GI dysfunction and immobility [1–4]. However, the use of opioids has been associated with a risk of suppressing GI motility and increasing PONV, inhibiting patients' activity of daily living despite the acceptable efficacy for pain control. As a postoperative pain management strategy for the ERAS protocol, thoracic epidural analgesia remains the gold standard for esophagectomy, providing better pain relief than systemic opioids [15]. However, there are no reports that reducing the opioids contained in the epidural anesthesia leads to enhanced recovery after surgery. In the present report, the concomitant use of scheduled intravenous acetaminophen significantly decreased the use of opioids and other analgesics, such as NSAIDs and pentazocine. With the reduced use of opioids, a significant reduction in the incidence of PONV and the enhanced motility of the GI tract were confirmed in the A-group. The GI motility of patients who undergo ileocolon reconstruction tends to become weak because of the wide range of mobilization approaches and high number of anastomoses [16]. However, there are no significant differences in the GI motility between gastric tube reconstruction and ileocolon reconstruction, No significant differences in PONV were noted between the reconstruction organs. This new pain control strategy may contribute to early ambulation after esophagectomy and reduce the duration of ICU stay and postoperative hospital stay, which are influenced by social factors such as the bed occupancy rate.

Furthermore, the assessment of the patients' pain is generally achieved using a visual analog scale (VAS). However, in the present study, we use the number of PCA pushes to assess patients' pain. Epidural anesthesia was administered in this study as a continuous infusion of ropivacaine and fentanyl at a rate of 2–5 ml/h, depending on pain intensity, with 1–3 ml PCA as rescue analgesia. When the patients feel postoperative pain, they push the PCA button themselves. Based on the findings in the present study, we feel that the number of PCA pushes may be useful as a new way to assess patients' pain as an alternative to the VAS.

Potential limitations associated with this study include its retrospective nature using historical controls and relatively limited number of patients after propensity score matching. However, the approach to perioperative management during

the study period was similar except for with regard to the pain management, and the current data are based on a prospectively collected database for consecutive patients in a relatively short term. In addition, a significant reduction in opioid use, PONV and GI dysfunction seem to have a strong association with an enhanced recovery and decreased duration of hospital stay after esophagectomy. External validation study using a larger number of patients will be needed to confirm the current observations.

Conclusion

Scheduled postoperative intravenous acetaminophen after esophagectomy may reduce the use of opioids and might be associated with enhanced GI motility and a decreased incidence of PONV. Scheduled intravenous acetaminophen may be a feasible new pain management option for the ERAS protocol after esophagectomy.

Acknowledgements We thank Dr. Erika Ohkura for her English proofreading of our manuscript.

Author contributions Study conception: YO, JS, and MU. Data accumulation: all authors. Data analysis: YO, JS, and MU. Writing of the manuscript: all authors. Critical revision: YO, JS, MU, and HU.

Compliance with ethical standards

Informed consent Written informed consent was obtained from all of the patients for the publication of this report.

Conflict of interest All authors have no conflicts of interest or financial ties to disclose.

References

1. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhauq A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr. 2005;24(3):466–77.
2. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248(2):189–98.
3. Jensen K, Kehlet H, Lund CM. Post-operative recovery profile after laparoscopic cholecystectomy: a prospective, observational study of a multimodal anaesthetic regime. Acta Anaesthesiol Scand. 2007;51(4):464–71.
4. Ohkura Y, Haruta S, Shindoh J, Tanaka T, Ueno M, Udagawa H. Effectiveness of postoperative intravenous acetaminophen (Acelio) after gastrectomy: a propensity score-matched analysis. Medicine (Baltimore). 2016;95(44):e5352.
5. Sobin LH, Gospodarowicz MK, Wittekind C, editors. International Union Against Cancer. Oesophagus including oesophagogastric junction. "TNM classification of malignant tumours". West Sussex: Wiley-Blackwell; 2009. pp. 66–72.
6. Candiotti K, Singla N, Wininger S. A randomized, double-blind, placebo-controlled, multi-center, parallel-group, multiple-dose study of the efficacy and safety of intravenous acetaminophen over 48 h for the treatment of postoperative pain after gynecologic surgery. In: American Society of Regional Anesthesia & Pain Medicine, 33rd Annual Spring Pain Meeting & Work shops; 2008.
7. National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Publish: May 28, 2009 (v4.03: June 14, 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
8. Akiyama H, Miyazono H, Tsurumaru M, Hashimoto C, Kawamura T. Use of the stomach as an esophageal substitute. Ann Surg. 1978;188:606–10.
9. Udagawa H, Ueno M, Kinoshita Y. Rationale for video-assisted radical esophagectomy. Gen Thorac Cardiovasc Surg. 2009;57:127–31.
10. Udagawa H, Ueno M, Shinohara H, Haruta S, Nakagawa M, Tsurumaru M. The importance of grouping of lymph node stations and rationale of three-field lymphoadenectomy for thoracic esophageal cancer. J Surg Oncol. 2012;106(6):742–7.
11. Ohkura Y, Ueno M, Iizuka T, Haruta S, Tanaka T, Udagawa H. Factors predicting effectiveness of neoadjuvant therapy for esophageal squamous cell carcinoma. Medicine (Baltimore). 2016;95(15):e3365.
12. Bjorkman DJ, Kimmey MB. Non steroidal anti-inflammatory drugs and gastrointestinal disease: pathophysiology, treatment and prevention. Dig Dis. 1995;13(2):119–29.
13. Scott G, Susan F. Use of intravenous acetaminophen in the treatment of postoperative pain. J Peri Anesthesia Nurs. 2011;26(2):74–80.
14. Zafar N, Davies R, Greenslade GL, Dixon AR. The evolution of analgesia in an 'accelerated' recovery programme for resectional laparoscopic colorectal surgery with anastomosis. Colorectal Dis. 2010;12:119–24.
15. Findlay JM, Gillies RS, Millo J, Sgromo B, Marshall RE, Maynard ND. Enhanced recovery for esophagectomy: a systemic review and evidence-based guidelines. Ann surg. 2014;259(3):413–31.
16. Honda M, Daiko H, Kinoshita T, Fujita T, Shibasaki H, Nishida T. Minimally invasive resection of synchronous thoracic esophageal and gastric carcinomas followed by reconstruction: a case report. Surg Case Rep. 2015;1(1):12.